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## Effects of Amlodipine and Lisinopril on Left Ventricular Mass and Diastolic Function in Previously Untreated Patients with Mild to Moderate Diastolic Hypertension

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**Beltman FW, Heesen WF, Smit AJ, May JF, de Graeff PA, Havinga TK, Schuurman FH, van der Veur E, Lie KI, Meyboom-de Jong B.** *Effects of amlodipine and lisinopril on left ventricular mass and diastolic function in previously untreated patients with mild to moderate diastolic hypertension.* Blood Pressure 1998; 7: 109–117.

The aim of the study was to compare the effects of two long-acting antihypertensive agents, the calcium-antagonist amlodipine and the ACE inhibitor lisinopril, on left ventricular mass and diastolic filling in patients with mild to moderate diastolic hypertension from primary care centres. It is a 1-year prospective, double-blind, randomized, parallel group, comparative study. Patients between 25 and 75 years of age with untreated hypertension with elevated diastolic blood pressure ( $\geq 95$  mmHg) on three occasions (twice on the first visit and once only on the second and third visits) were recruited from a population survey. After 4 weeks placebo run-in 71 patients were randomized to dosages of amlodipine 5–10 mg or lisinopril 10–20 mg, which were titrated on the basis of the effects on blood pressure. Fifty-nine patients completed the study period. Primary endpoints were left ventricular mass index and early to atrial peak filling velocity. Office and ambulatory blood pressure and other echocardiographic measurements were considered secondary. Decrease in blood pressure was equal for both treatment regimens. A statistically significant decrease in left ventricular mass index in both treatment groups was observed:  $-11.0$  g/m<sup>2</sup> (95% CI:  $-6.0$ ,  $-16.1$ ) in the amlodipine group and  $-12.6$  g/m<sup>2</sup> (95% CI:  $-8.2$ ,  $-17.0$ ) in the lisinopril group. The higher the baseline value of left ventricular mass before treatment, the more the decrease after treatment. Early to atrial peak filling velocity did not change significantly within the treatment groups:  $+0.07$  (95% CI:  $-0.01$ ,  $+0.15$ ) in the amlodipine group and  $+0.01$  (95% CI:  $-0.06$ ,  $+0.08$ ) in the lisinopril group. However, analysis of time measurements of the early peak showed significant changes for both treatment groups. No significant differences in primary and secondary endpoints between treatment groups were found. Twelve patients did not complete the study, seven in amlodipine and five in lisinopril, basically due to adverse events. The effects of amlodipine and lisinopril on left ventricular mass and early to atrial filling peak velocity after 1 year of treatment in patients with previously untreated mild to moderate hypertension are similar. Further studies are recommended, particularly with a larger sample size and a follow-up of longer duration. **Key words:** *angiotensin-converting enzyme inhibitor, calcium-antagonist, hypertension, diastolic function, left ventricular hypertrophy, randomised controlled trial.*

### INTRODUCTION

In hypertensive patients, left ventricular hypertrophy is an important cardiovascular risk factor and there is growing evidence that regression of left ventricular mass is an important goal of treatment [1–4]. A recent meta-analysis [5] did not find any significant difference between angiotensin converting enzyme (ACE) inhibitor and calcium blocker, but in a multicentre study in hypertensive men Gottdiener et al. [6] found the best effect in the left ventricular was with ACE inhibitor and diuretics and that results with the calcium channel blocker diltiazem were disappointing. These results have to be interpreted

with caution: the majority of the studies included in this meta-analysis were open, uncontrolled, single-drug studies, and they also differed in methodology with respect to selection of patients, duration of follow-up, treatment schedule, and echocardiographic methodology [7, 8]. Some of the interpretation problems can be avoided if only prospective, double-blind, randomized controlled trials, with a parallel group design are taken into account [7]. Only a few studies of this type compare ACE inhibitors and calcium antagonists [6, 8–10], and some of them cannot be considered trials for definite conclusions about inter-agent differences because of methodological limitations [11].

Besides measurement of left ventricular mass, Doppler echocardiography is often used to measure diastolic filling abnormalities non-invasively in assessing diastolic dysfunction. This is a common abnormality in mild to early hypertension. Diastolic dysfunction is frequently seen in the presence of left ventricular hypertrophy, but this may also occur independently of the hypertrophic process [12]. Long-term treatment of hypertension has been shown to improve diastolic function, even in the absence of left ventricular hypertrophy. In general, the data suggest a beneficial effect of calcium antagonists and ACE inhibitors, but not of beta-blockers or diuretics [12].

The primary objective of this 1-year prospective, double-blind, randomized, parallel group, comparative study was to compare the effects of two long-acting antihypertensive agents, the calcium-antagonist amlodipine and the ACE inhibitor lisinopril, on left ventricular mass and diastolic filling in patients with mild to moderate diastolic hypertension. Secondary objectives were comparison of antihypertensive efficacy, safety and tolerability of both drugs.

## METHODS

### *Patient selection*

Untreated, newly diagnosed patients with diastolic hypertension were recruited from a population survey. Blood pressure was measured in the sitting position after 5 min of rest using the right arm. Systolic (SBP) and diastolic (DBP) blood pressure were recorded at Korotk-off phases I and V at the nearest 2 mmHg. If a difference in blood pressure was found between both arms ( $>5/10$  mmHg for DBP and SBP, respectively), the one with the highest blood pressure was used for further measurement. Both male and female patients with diastolic hypertension (DBP  $\geq 95$  mmHg on three different occasions, e.g. twice on the first occasion and once on the second and third occasions; the blood pressures were assessed within a period of 4 weeks and average DBP  $< 115$  mmHg during a period), between 25 and 75 years of age, from the primary healthcare system were included in the study and received placebo treatment during 4 weeks. Exclusion criteria were: DBP not stable after placebo-treatment period (difference with DBP before placebo treatment  $>10$  mmHg), secondary or malignant hypertension, angina pectoris, haemodynamically significant valvular cardiac disease, insulin and non-insulin dependent diabetes mellitus, and women of child-bearing potential. All patients gave their written informed consent and the protocol was approved by the Medical Ethics Committee of the University Hospital Groningen.

### *Double-blind treatment phase*

After the placebo treatment period of 4 weeks (during

which the patients were seen twice, 0 and at 4 weeks), and if DBP was stable, patients were randomized to double-blind treatment with amlodipine 5 mg or lisinopril 10 mg. Patients who did not meet the therapeutic response (reduction in the average sitting DBP to a value of  $\leq 90$  mmHg or a fall from baseline of at least 10 mmHg to a value of  $\leq 100$  mmHg) after 4 weeks of active treatment were adjusted to the double dose. After 6 weeks of treatment the dose remained unchanged. Patients who did not meet the therapeutic response after 12 weeks were excluded. Compliance of treatment was followed by counting returned tablets at various visits.

### *Office and ambulatory blood pressure measurements*

Office blood pressure (OBP) was measured in the sitting position twice every visit (4, 6, 12, 26 and 52 weeks after start of active treatment) at a 2-minute interval. The mean of two measurements was used. Ambulatory blood pressure (ABP) was measured at baseline and after 1 year of treatment using the SpaceLabs 90207 equipment (SpaceLabs Inc. Redmond, Washington, USA). The non-dominant arm was used, but if a difference in OBP between either arm was found, the one with the highest blood pressure was used. ABP was recorded every 30 min during daytime (7.00–22.59 h) and at every 60 min (because it has been shown that daytime ambulatory blood pressure has more prognostic value) during night-time (23.00–6.59 h), the study being in primary healthcare. Ambulatory measurements started 30–60 min before medication intake. Patients should not have missed any scheduled dosage within the 24 h prior to blood pressure measurements. ABP data were analysed without data-editing using time-weighted blood pressures for 24-h; daytime and night-time were calculated [14].

### *Echocardiography*

All echocardiographic examinations at baseline and after 1 year of treatment were performed by the same observer, who was unaware of the identity of patients or BP measurement. An Acuson XP 128 echocardiograph (Acuson Corp., USA) was used with a 2.0 or 2.5 MHz transducer. Mean values of three recordings were used. Left ventricular dimensions were measured in two-dimensional mode in accordance with the Penn convention in the left lateral decubitus position in the third or fourth intercostal space. Measurements of end diastolic left ventricular posterior wall (LVPW), interventricular septum (IVS) and left ventricular end diastolic diameter (LVEDD) were made. To estimate the left ventricular mass (LVM) the formula of Devereux [15] was used:  $LVM(g) = 1.04 \{ (LVPW + IVS + LVEDD)^3 - (LVEDD)^3 \} - 13.6$ . LVM was divided by body surface area (in metres squared) to calculate LVM index (LVMI).

Table I. Baseline characteristics of the 71 randomized patients

	Amlodipine (n = 35)	Lisinopril (n = 36)
Age (years)	53 ± 10	54 ± 11
Sex (% male)	51	72
Body mass index (kg/m <sup>2</sup> )	27.2 ± 4.3	27.8 ± 3.4
Office SBP/DBP (mmHg)	158 ± 16/102 ± 5	161 ± 15/100 ± 4
Heart rate (bpm)	81 ± 12	82 ± 11

SBP/DBP = systolic/diastolic blood pressure, values are mean ± standard deviation.

Left ventricular hypertrophy was defined as: LVMI ≥ 108 g/m<sup>2</sup> for women and ≥ 118 g/m<sup>2</sup> for men [16].

Diastolic filling abnormalities were measured with pulsed Doppler echocardiography. Measurements were made in the standard apical four-chamber view with the patient in the left decubitus position. The Doppler sampling volume was placed between the tips of the mitral valve leaflets to obtain maximal filling velocities. Three recordings were made, end-expiratory. Measurements were performed with the Acuson calculation software package. Early and atrial peak filling velocities (E-peak and A-peak) were measured and their ratio (E/A ratio) was calculated. Time measurements of the early filling phase were performed: early acceleration time (EAT), early deceleration time (EDT) and pressure half time (PHT). Isovolumetric relaxation time (IVRT) was measured as time between the end of aortic outflow signal and beginning of mitral inflow signal in a standard five-chamber view.

To study the tolerance of study drugs, the patients were given a questionnaire and any other untoward event that they reported was recorded.

#### Statistical analysis

Monitoring and statistical analysis (the SAS software package) of the study was performed by an independent monitoring agency (IMRO BV, The Netherlands). Primary endpoints were LVMI and E/A ratio. All other parameters were considered to be secondary. Results are expressed as mean ± standard deviation (SD). A two-tailed  $p < 0.05$  was considered statistically significant. To test for changes within and differences between treatment groups, an analysis of variance (ANOVA) was carried out with the changes in endpoints as dependent variables, and treatment group and sex as fixed factors. Sex was dropped from the model if it was not significant and the statistical test then reduced to a  $t$ -test. Additionally, an analysis of covariance (ANCOVA) was carried out with correction for the baseline values of the primary and secondary endpoints (continuous covariate). If there was a significant relation with the baseline value it was also tested

whether the relation with baseline was equal (equality of slopes) for both treatment groups. An intention-to-treat analysis (including all randomized patients) was performed. Only in the case of a large number of protocol violators (>10%), was a per protocol analysis performed (including all patients who completed the protocol).

To study the relation between changes in office and ambulatory blood pressure and changes in LVMI and E/A ratio, an ANCOVA was carried out. Estimates (with 95% confidence interval) of the effect of change in blood pressure on the change in LVMI and E/A ratio were calculated. The changes in systolic and diastolic values of the office and ambulatory blood pressure were included separately because of the large correlation between these blood pressures. The increase in fit of the model after inclusion of the blood pressure was used as a measure of correlation. To study the relation between change in LVMI and change in E/A ratio, a Pearson correlation coefficient was calculated.

#### RESULTS

Patient's characteristics of both treatment groups are given in Table I. There was a difference in the distribution of sex, however, and slightly higher body mass index in the lisinopril group might be a consequence of this finding.

In the amlodipine and lisinopril groups, 16 of 35 (46%) and 15 of 36 (42%) patients, respectively, were adjusted to the higher dose of 10 and 20 mg. After 1 year, office blood pressures were available for 69 (97%) patients, ambulatory blood pressures for 59 (83%) patients, and echocardiographic measurements of LVMI and E/A ratio were available for 57 (80%) and 59 (83%), respectively. Of the total of 59 who completed the study, 28 were in the amlodipine group (80%) and 31 in the lisinopril group (86%). Reasons for not completing the study in the amlodipine group ( $n = 7$ ) were: ankle oedema (1), exanthema (1), pustulae (1), withdrawal of informed consent (3) and no therapeutic response after 12 weeks of treatment (1). Reasons for not completing the study in the lisinopril group ( $n = 5$ ) were: hyperkalaemia (1), dys-

Table II. Baseline values and changes after 1 year of treatment for office and ambulatory (ABP) blood pressure

		Amlodipine		Lisinopril	
		Baseline	Change 1 year (CI)	Baseline	Change 1 year (CI)
Office BP	SBP	157.7 ± 16.3	-14.9 (-9.4, -20.4)*	161.3 ± 14.6	-15.6 (-10.8, -20.4)*
	DBP	102.0 ± 5.2	-12.4 (-9.7, -15.1)*	100.1 ± 3.5	-9.2 (-7.0, -11.5)*
	HR	81.0 ± 12.2	-9.7 (-5.9, -13.5)*	82.4 ± 11.1	-9.5 (-4.6, -14.5)*
24h-ABP	SBP	140.8 ± 14.3	-15.3 (-10.2, -20.3)*	137.5 ± 11.1	-15.0 (-11.0, -19.0)*
	DBP	90.1 ± 10.7	-9.8 (-6.4, -13.2)*	87.2 ± 8.1	-9.9 (-7.3, -12.5)*
	HR	76.3 ± 7.8	-2.4 (0.1, -4.9)	75.6 ± 7.2	-2.0 (-4.3, 0.3)
Day-ABP	SBP	145.7 ± 13.3	-15.2 (-10.5, -20.0)*	144.1 ± 11.5	-15.7 (-11.0, -20.4)*
	DBP	95.1 ± 10.4	-10.2 (-6.9, -13.4)*	92.8 ± 8.6	-10.7 (-7.7, -13.7)*
	HR	80.9 ± 8.7	-2.2 (1.0, -5.3)	79.9 ± 8.4	-2.0 (0.9, -4.9)
Night-ABP	SBP	130.5 ± 19.4	-15.3 (-8.7, -22.0)*	124.1 ± 14.3	-13.0 (-8.8, -17.1)*
	DBP	79.9 ± 13.0	-9.0 (-4.4, -13.7)*	75.7 ± 9.9	-8.3 (-5.3, -11.3)*
	HR	67.0 ± 7.3	-3.0 (-0.8, -5.1)*	67.0 ± 6.9	-1.0 (-3.2, 1.2)

ABP = ambulatory blood pressure (in mmHg), SBP = systolic blood pressure (in mmHg), DBP = diastolic blood pressure (in mmHg), HR = heart rate (in bpm), CI = 95% confidence interval, \* = statistically significant change with respect to baseline ( $p < 0.05$ ). No differences between treatment groups except for office DBP (see text), values are mean ± standard deviation.

pnouea (1), angina pectoris (2) and withdrawal of informed consent (1). All the patients were included in the intention-to-treat analysis.

derived blood pressures, during daytime, night-time and 24-h, were not significantly different between treatment groups.

#### Office and ambulatory blood pressure response

The office and ambulatory blood pressures at baseline and the changes after 1 year of treatment are given in Table II. Systolic and diastolic office blood pressures and heart rate decreased significantly in both treatment groups. For diastolic blood pressure there was a significant interaction between treatment group and sex ( $p = 0.02$ ). For females, there was a difference in the change in diastolic blood pressure between amlodipine and lisinopril in favour of amlodipine. No differences existed between amlodipine and lisinopril in the change in office systolic blood pressure and heart rate. The changes in ambulatory-

#### Echocardiographic measurements

The baseline values of, and the changes in, the left ventricular dimensions and left ventricular mass estimates are given in Table III. The percentages of patients with left ventricular hypertrophy in the amlodipine and lisinopril group was 14% and 9%, respectively. There was a statistically significant decrease in LVMI in both treatment groups:  $-11.0 \text{ g/m}^2$  (95% CI:  $-6.0, -16.1$ ) in the amlodipine group and  $-12.6 \text{ g/m}^2$  (95% CI:  $-8.2, -17.0$ ) in the lisinopril group. Septal and posterior wall thickness decreased significantly, whereas end-diastolic diameter increased significantly in both treatment groups.

Table III. Left ventricular mass and dimensions, and weight at baseline and absolute change after 1 year of treatment for each treatment group

	Amlodipine		Lisinopril	
	Baseline	Change 1 year (CI)	Baseline	Change 1 year (CI)
LVMI ( $\text{g/m}^2$ )	87.5 ± 21.1	-11.0 (-6.0, -16.1)*	90.6 ± 16.2	-12.6 (-8.2, -17.0)*
IVS (mm)	9.6 ± 1.2	-1.4 (-1.0, -1.7)*	10.0 ± 1.1	-1.2 (-0.8, -1.5)*
LVPW (mm)	9.5 ± 1.2	-1.2 (-0.9, -1.6)*	9.9 ± 1.0	-1.3 (-1.0, -1.7)*
LVEDD (mm)	44.9 ± 4.8	+2.5 (+1.5, +3.4)*	45.3 ± 4.2	+1.2 (+0.5, +1.9)*
LVM (g)	168.2 ± 44.5	-20.4 (-10.7, -30.0)*	179.0 ± 36.8	-24.6 (-15.9, -33.2)*
Weight (kg)	79.6 ± 11.5	0.9 (+0.0, +1.7)*	83.2 ± 12.0	0.6 (-0.0, +1.3)

LVM(I) = left ventricular mass (index), IVS = interventricular septum, LVPW = left ventricular posterior wall, LVEDD = left ventricular end diastolic diameter. CI = 95% confidence interval, \* = statistically significant change with respect to baseline ( $p < 0.05$ ). No differences between treatment groups. Values are mean ± standard deviation.

Table IV. Left ventricular filling parameters at baseline and absolute change after 1 year of treatment for each treatment group

	Amlodipine		Lisinopril	
	Baseline	Change 1 year (CI)	Baseline	Change 1 year (CI)
E-peak (m/s)	0.76 ± 0.12	+0.02 (−0.03,+0.07)	0.70 ± 0.12	+0.01 (−0.02,+0.05)
A-peak (m/s)	0.75 ± 0.13	−0.02 (−0.04,+0.01)	0.76 ± 0.13	+0.01 (−0.02,+0.04)
E/A-ratio	1.04 ± 0.24	+0.07 (−0.01,+0.15)	0.95 ± 0.27	+0.01 (−0.06,+0.08)
EAT (ms)	98.1 ± 13.2	+2.0 (−3.9,+7.9)	102.1 ± 14.4	+3.0 (−2.0,+8.0)
EDT (ms)	208.5 ± 29.4	−24.5 (−36.7,−12.4)*	215.1 ± 36.6	−22.6 (−34.0,−11.0)*
PHT (ms)	61.3 ± 8.5	−7.3 (−10.8,−3.7)*	63.1 ± 10.7	−6.7 (−10.0,−3.5)*
IVRT (ms)	106.0 ± 17.0	−3.0 (−8.3,+2.4)	108.5 ± 13.3	−6.5 (−11.8,−1.2)*
HR (bpm)	68.6 ± 9.2	−3.8 (−6.8,−0.7)*	68.7 ± 8.2	−1.0 (−4.4,+2.4)

E-peak, A-peak and E/A-ratio = early and atrial peak filling velocity and their ratio, EAT = early acceleration time, EDT = early deceleration time, PHT = pressure half time, IVRT = isovolumetric relaxation time, HR = heart rate. CI = 95% confidence interval, \* = statistically significant change with respect to baseline ( $p < 0.05$ ). No differences between treatment groups. Values are mean ± standard deviation.

No statistically significant differences were found between the groups. The percentage of patients with left ventricular hypertrophy after treatment was zero in both treatment groups. The changes in LVMI, IVS, LVPW and LVEDD were significantly related to the baseline value of these parameters ( $p = 0.0001$ ): the higher the baseline value, the more the decrease after treatment. These relations were similar for both treatment groups ( $p = 0.83$ – $0.91$ ) and there was no difference in weight between either group.

Diastolic filling parameters at baseline and their changes after 1 year of treatment are given in Table IV. E/A ratios before treatment in the amlodipine and lisinopril groups were 1.04 and 0.95, respectively. No change in E-peak, A-peak or their ratio (E/A ratio) was seen in either treatment group. Early deceleration time (EDT) and pressure half time (PHT) decreased in both treatment groups. In the lisinopril group a significant decrease in isovolumetric relaxation time (IVRT) was

seen as well. Heart rate (HR) decreased significantly in the amlodipine group. Early acceleration time (EAT) remained unchanged for both treatment groups. No statistically significant differences between either treatment group were found. There was no significant relation between the baseline value of the E/A ratio and the change in E/A ratio after treatment ( $p = 0.65$ ). Changes in all secondary parameters (except for A-peak:  $p = 0.45$ ) were significantly related to their baseline value ( $p = 0.0001$ ): the more disturbance in these parameters before treatment, the more improvement after intervention. For the PHT, this relation was significantly stronger for patients treated with amlodipine in comparison with patients treated with lisinopril:  $p = 0.049$ .

#### Relations between changes in blood pressure, LVMI and E/A ratio

Results of an analysis of covariance assessing the

Table V. Relations between changes in LVMI and E/A ratio, and changes in office and ambulatory blood pressures

		Estimate (CI)	$\Delta R^2$
LVMI	Office SBP	+0.17 (−0.04,+0.38)	0.046
	Office DBP	+0.48 (+0.02,+0.94)	0.076
	24 h SBP	+0.43 (+0.18,+0.68)	0.178
	24 h DBP	+0.67 (+0.29,+1.05)	0.192
E/A ratio	Office SBP	−0.0033 (−0.0066,+0.0000)	0.063
	Office DBP	−0.0125 (−0.0193,−0.0057)	0.182
	24 h SBP	−0.0075 (−0.0109,−0.0041)	0.228
	24 h DBP	−0.0112 (−0.0164,−0.0060)	0.225

LVMI = left ventricular mass index, E/A ratio = early to atrial peak filling velocity ratio, SBP = systolic blood pressure, DBP = diastolic blood pressure. Estimate: estimate of the effect of change in blood pressure (mmHg) on change in LVMI ( $\text{g}/\text{m}^2$ ) and E/A ratio (e.g. 1 mmHg rise in 24 h DBP is related to a change in LVMI of 0.67  $\text{g}/\text{m}^2$ );  $\Delta R^2$ : increase in fit of the model after including the blood pressure separately, CI = 95% confidence interval.

Table VI. Published randomized controlled trials (without non-pharmacological intervention, classified by type of blinding), with a parallel group design, comparing ACE inhibitors and calcium antagonists in mild to moderate essential hypertension (DBP  $\geq$  95 mmHg)

Study	Agent (daily dose in mg)	N included	Follow-up (weeks)	Monotherapy	ΔLVMI	ΔE/A
Randomized, parallel group comparative studies: double-blind						
[8] <sup>##</sup>	Nifedipine SR (40–80)	20	24	no, HCT added	−16%***	−
[9] <sup>!</sup>	Perindopril (4–8)	20	24	no, HCT added	−14%***	−
	Nifedipine (40)	15			−9%***	−
[10] <sup>!</sup>	Fosinopril (20)	16	12	yes	−15%***	+2%
	Isradipine (5)	13			−12%**	
	Enalapril (20)	13			−4%	
Present study <sup>§,##</sup>	Amlodipine (5–10)	35	52	yes	−13%***	+7%
	Lisinopril (10–20)	36			−14%***	+1%
Randomized, parallel group comparative studies: blinding of echocardiography						
[19] <sup>##</sup>	Isradipine (2.5–5)	16 <sup>&amp;</sup>	16	yes	−9% <sup>#</sup>	+7%
	Lisinopril (10–40)	16 <sup>&amp;</sup>			−9% <sup>#</sup>	+11%
[31]	Amlodipine (5–10)	12	26	yes	−16%*	+6%
	Enalapril (10–20)	12			−15%*	+10%
Randomized, parallel group comparative studies: no blinding						
[18]	Nitrendipine (20–40)	67 <sup>&amp;</sup>	104	yes	−26%**	+66%**
	Captopril (75–100)	67 <sup>&amp;</sup>			−26%**	+49%**
[20]	Nitrendipine (20–40)	15 <sup>@</sup>	38	yes	−14%***	−1%
	Captopril (50–100)	18 <sup>@</sup>			−21%***	+15%*
[21]	Nifedipine (20–40)	8	26	yes	−13%*	−
	Captopril (50–100)	8			−12%*	−

$\Delta$ LVMI = change in left ventricular mass index;  $\Delta$ E/A = change in E/A ratio, HCT = hydrochlorothiazide. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ , #  $p < 0.001$  within study population, ## statistically significant relation between change in blood pressure and change in LVMI, @ analysed patients, § previously untreated patients, & patients selected on DBP and SBP. ! Statistically significant difference in  $\Delta$ LVMI between treatment groups.

relationships between the changes in office and ambulatory blood pressures and the changes in primary endpoints are given in Table V. A decrease in 24-h ambulatory blood pressures is related to a decrease in LVMI. The change in the fit of the model after the change in blood pressure was added is given by  $\Delta R^2$ . However, the differences were not statistically significant. There was no significant relation between changes in LVMI and E/A ratio ( $r = -0.15$ ;  $p = 0.26$ ).

#### Adverse events

Adverse events related to the therapy occurred in 6 patients (17%) of the amlodipine group and in 7 (19%) of the lisinopril group. The most frequently observed adverse events were peripheral oedema in five patients (14%) of the amlodipine group and dizziness in four patients (11%) of the lisinopril group. The overall incidence of adverse events was considerably higher when adverse events of unknown relationship were

added: 69% in the amlodipine group and 58% in the lisinopril group. There was no evidence of a difference between the two treatment groups with respect to the number of patients with adverse events.

#### DISCUSSION

This study shows that the effects of amlodipine and lisinopril on left ventricular mass and diastolic filling after 1 year of treatment in patients with previously untreated mild to moderate hypertension are similar. Left ventricular mass index in both treatment groups decreased significantly after 1 year of treatment:  $-11.0 \text{ g/m}^2$  and  $-12.6 \text{ g/m}^2$  in the amlodipine and lisinopril groups, respectively. No significant changes in E/A ratio were seen.

In females, amlodipine decreased office diastolic blood pressure better than lisinopril, but ambulatory blood pressure data showed equal changes in diastolic blood pressures for amlodipine and lisinopril. Because the reproducibility of ambulatory blood pressure is superior

to that of the office blood pressure, the blood pressure decrease in both treatment groups was considered to be equal [17].

#### *Comparison with other studies*

The results of eight published randomized controlled trials concerning the effects on LVMI and comparing ACE inhibitors and calcium antagonists are given in Table VI. According to recently designed criteria for trials on regression of left ventricular hypertrophy, none of these eight published studies can be considered a trial for definite conclusions about inter-agent differences [11]. All studies were randomized, between-agent comparisons, in women and men, and used echocardiography to assess regression of left ventricular hypertrophy (selection criteria used). However, only three [8–10] were double-blind, only one [18] had a sufficient follow-up (1 year), and five of eight studies [8, 18–21] analysed relations between changes in blood pressure and changes in LVMI. The present study fulfilled all the criteria mentioned above and, in addition, was the only study which included previously untreated patients. There are no studies, including the present, which fulfilled the last two criteria: including an ethnically diverse population and at least 150–200 patients per treatment arm. To exclude the possibility of inter-agent differences, it is indeed important to include larger numbers of patients. The relatively large 95% confidence intervals of the differences in LVMI in both treatment groups found in the present study also point at a non-optimal precision. Even Dahlöf et al. [22], in their meta analysis comprising over 2000 patients also ran into some problems, e.g. only 17% of the studies were randomized, follow-up was on average 10 months and number of patients per study was average 21, etc. More accurate estimates of the effects can be obtained from meta-analyses of well-designed parallel group comparative studies. The compiled data of the studies summarized in Table VI suggest that there are no differences between calcium antagonists and ACE inhibitors with respect to regression of LVMI. Devereux and Dahlöf [11] have suggested the following types of studies for the future for establishing the therapeutic usefulness of treating LVH *per se* and not just for lowering the blood pressure: (1) Medium-sized studies with 300–400 patients followed up for at least 6 months to determine definitively whether inter-agent differences in reduction of LV mass exist, and (2) large, long-term trials with at least 1200 patients followed up for a minimum of 4 years to determine whether LVH reversal improves prognosis over and above blood pressure reduction and the type of treatment used.

In only two [8, 19] of the eight studies summarized in Table VI, a significant relation between changes in blood

pressure and changes in LVMI could be found. In the present study, the changes in LVMI were significantly related to the changes in blood pressure and this relation proved to be stronger for ambulatory blood pressure than for office blood pressures. If regression of LVMI is considered to be a good predictor of prognosis, these results suggest that prognosis is more strongly related to changes in ambulatory blood pressures.

#### *Diastolic filling*

Regression of left ventricular mass is usually associated with improvement of diastolic filling. In this study, E/A ratio did not change significantly; changes in E/A ratio were not related to the pretreatment level, and there was a very weak relation between changes in LVMI and changes in E/A ratio. These results may be explained by the fact that in neither of the treatment groups was E/A ratio markedly abnormal before the start of treatment. It can be seen from Table VI that statistically significant changes in E/A ratio were seen in only two of six studies [18, 20].

The lack of hypertrophy at baseline in the majority of our patient population is comparable to that in the TOMHS study [24], J. D. Neaton et al.'s work [25] and the latest issue of *Circulation* (1997) [6]. We would like to point out that prevalence of hypertrophy in mild to moderate hypertension in these primary care patients is very low.

In this study, no differences were found in the changes in isovolumetric relaxation time (IVRT) (decreased significantly during lisinopril treatment but not in response to amlodipine), peak early filling (E-peak) and early acceleration time (EAT) within the groups. However, the changes in IVRT, E-peak and EAT were significantly related to their baseline values, which means that improvement can be seen after treatment with both agents at higher levels of dysfunction. Deceleration of the early filling velocity is strongly related to left ventricular compliance [22]. In both treatment groups, significant and similar changes in early deceleration time (EDT) and pressure half time (PHT) were seen, whereas peak early filling (E-peak) remained unchanged. Furthermore, changes in EDT and PHT were significantly related to the baseline values. Thus, although the E/A ratio remained unchanged, the analysis of these secondary parameters shows that both amlodipine and lisinopril alter diastolic filling and that improvement of diastolic filling is dependent on the level of impairment before treatment.

As far as the mechanism of regression of LVH is concerned, in the experimental studies it has been shown that pharmacologic agents that interfere with the adrenergic nervous system may induce regression in myocardial mass due to reduction in myocyte size, but



with unchanged or even increased myocardial collagen concentration [26]. Treatment of spontaneously hypertensive rats with the ACE inhibitor lisinopril resulted in a complete normalization of this remodelling, including coronary flow reserve [27]. Similar findings have been observed with captopril [28] and the calcium antagonist nifedipine [29].

Thus, based upon experimental experience, adrenergic blocking drugs seem to induce regression of LVH mainly by reducing myocyte hypertrophy, whereas calcium antagonists and ACE inhibitors may have favourable effects on structural myocardial and coronary artery remodelling as well.

The higher incidence of adverse events reported in our study and withdrawal from the study are not uncommon, particularly when a questionnaire recording adverse events is used.

## CONCLUSION

The effects of amlodipine and lisinopril on left ventricular mass and E/A ratio after 1 year of treatment in patients with previously untreated mild to moderate hypertension are similar. Left ventricular mass index in both treatment groups decreased significantly whereas the E/A ratio did not change. The compiled results of the present study and those of other published clinical trials suggest that there are no differences between calcium antagonists and ACE inhibitors with respect to regression of LVMI. But larger, controlled studies, as also suggested by Otterstad et al. [30], of various treatment regimens are still needed to demonstrate inter-drug differences and to establish whether drug-induced regression can improve the prognosis of hypertensive LVH independently or with the antihypertensive effect.

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